Uncovering neurodevelopmental features in bipolar affective disorder

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SUMMARY

Schizophrenia and bipolar disorder are genetically related and their clinical features overlap. Schizophrenia is conceptualized as a neurodevelopmental disorder but the evidence for bipolar disorder is less clear. Cluster-analytic approaches reveal different cognitive profiles within bipolar disorder, possibly reflective of differing neurodevelopmental loads, which are also suggested by recent genetic and neuroimaging studies. Such studies suggest the potential utility of further clinical subcategories in bipolar disorder based on neurodevelopmental load.

Background

Schizophrenia (SCZ) and bipolar disorder (BD) have historically been considered different entities but they co-segregate in families and genetic studies provide increasing evidence that they share risk alleles (1). Biological and clinical evidence of shared pathophysiology among major psychiatric disorders promoted the development of dimensional classifications such as Research Domain Criteria (RDoC). However, while SCZ shows neuropsychological and biological features of a neurodevelopmental disorder, the evidence for BD is less clear (4).

Neurodevelopmental disorders are characterized by early brain abnormalities, resulting from the impact of genetic and environmental factors on neurodevelopment. Such abnormalities increase the risk for the disorder, but overt symptoms may not become clinically manifest until a specific phase of development, when the brain regions involved reach functional maturity. However, subtle manifestations of pathology can be identified before clinical onset, presenting as delayed psychomotor milestones, neurological soft signs, abnormalities in sensory integration and deficits in several cognitive domains. These are associated with a variable degree of abnormalities observed in measures of brain morphology and connectivity (5).

Epidemiological, neuropsychological and neuroimaging evidence

Obstetric complications are one of the perinatal factors most strongly associated with SCZ while evidence of their role in BD is inconclusive (4). Some studies reported higher incidence and others no difference for BD patients relative to healthy controls (4). Mixed evidence also emerged from studies in BD high-risk offspring, though higher incidence was reported in a recent study, the first to include a comparison to healthy controls (6).

Cognitive impairments are one of the core clinical dimensions of SCZ. They are present premorbidly and are reliable predictors of long-term outcome. The distributed topography of their functional imaging correlates has led to their conceptualisation as a result of connectivity pathology, sustained by neuronal cell migratory abnormalities which are neurodevelopmental in origin (5). Deficits span across all neurocognitive domains, with the most significant impairments identified for executive function, verbal learning and processing speed (7). The same cognitive domains are the most impaired in BD both in euthymic and symptomatic phases, with most of the evidence suggesting a similar pattern but milder overall severity compared to SCZ (7). However a different longitudinal trajectory seems to characterise cognitive deficits in the two disorders: in SCZ, both retrospective reviews of patients' academic records and prospective studies showed premorbid general intellectual deficits (7) while the limited studies available in BD mainly reported good academic achievement in the years preceding illness onset (8). However, more recent studies suggest that examining population mean cognitive function may have masked increased risk at the extreme ends of premorbid scholastic achievement. Thus, in more recent studies, both poor and excellent school performance were associated with increased risk of later developing BD (9), suggesting that the timeframe of emergence of cognitive dysfunction may not be uniform and perhaps precede illness onset in those who underperform. Studies in high-risk cohorts robustly support the premorbid emergence of widespread cognitive impairment in SCZ (4). Evidence in BD high-risk cohorts is less conclusive, with some studies reporting impairments and others no differences compared to healthy controls (10). However, the modestly sized yet significant underperforming of youths at familial risk for BD identified in a recent meta-analysis (10) was considered to support the role of neurodevelopmental abnormalities in BD. The milder severity compared to SCZ high-risk populations may reflect a less pronounced developmental load in BD or result from possible dilution effects. In line with clustering analysis studies that have identified different cognitive profiles within BD, the results appear consistent with the existence of a BD subgroup with deficient pre-morbid cognitive function (10).

Neurological soft signs have been robustly identified in SCZ (11) but inconsistently in in BD (4). However a recent meta-analysis demonstrated a robust increase in BD, only moderately less severe than that observed in SCZ (11) and their presence has been identified in BD high-risk offspring (6).

In SCZ early signs of brain pathology manifest as structural brain abnormalities already present at illness onset (12). These are also observed in individuals at risk of developing the disorder (4), with a similar distribution yet milder severity compared to those observed at first episode. Findings are more heterogeneous in BD but meta-analytic evidence indicates that structural brain abnormalities are also present in first episode BD patients, though grey matter volume deficits appear less pronounced compared to SCZ (12). Morphological brain abnormalities have also been described in BD high-risk cohorts, yet findings have been more inconsistent compared to the evidence in populations at high-risk for SCZ (6).

Categorical and dimensional contributions to classification

Neurodevelopmental mechanisms are therefore either less pronounced in BD than in SCZ, or only pertain to a subgroup of BD patients. The RDoC approach proposes cognitive function as a trans-diagnostic domain to evaluate pathogenetic mechanisms of psychiatric disorders. The use of data clustering rather than diagnostic categories demonstrated that cognitive functioning across patients with SCZ and BD appeared distributed, albeit not evenly, over different clusters, ranging from no impairment to global and severe (13). Patients with SCZ were disproportionately more represented in the global impairment cluster, while patients with BD were less frequently characterised by widespread cognitive dysfunction. (13). This evidence raises the question of whether more severe cognitive dysfunction in BD is associated with a clinical picture closer to schizophrenia. A recent meta-analysis examined cognitive dysfunction between potential BD subtypes. BD type I significantly underperformed BD type II across most domains, as did BD with a history of psychosis relative to BD without psychosis. Cognitive differences between the groups were reported to be significant yet modest, hence raising questions about cognitive heterogeneity within BD being discriminatory between BD clinical subtypes (14).

Molecular imaging studies in schizophrenia have consistently shown increased striatal dopamine synthesis capacity (15). This was not observed in acute mania without psychosis (16). However a recent study in BD with psychosis revealed an increase in dopamine synthesis capacity similar to that observed in SCZ (17).

Further evidence regarding features potentially discriminating between BD with psychosis and BD without psychosis derives from polygenic risk score (PRS) analysis of common variants. Using this method, extensive genetic sharing has been observed

between SCZ and BD, but this is paired with growing evidence that differences between the two disorders also have a genetic basis (1). However a significant increase in SCZ PRS was observed for BP with psychosis compared to BD without psychosis (1) and associated with earlier age of onset (1).

The conceptualization of cross-disorder risk has recently been expanded beyond SCZ and BD, as population studies have also examined intellectual disability, autistic spectrum disorders (ASD) and attention deficit hyperactivity disorder (ADHD) (5). For these a gradient of neurodevelopmental pathology has been suggested, indexed by mutational load and cognitive impairment, with intellectual disability at the most affected end of the spectrum and BD at the other end (5). Different clinical pictures, rather than representing discrete constructs, are considered to lie on a continuum reflecting the severity and timeframe of the insult on the affected underlying brain circuitry (5).

PRS analyses capture common genetic variants but do not identify more rare ones, such as copy number variants (CNV). The latter were reported to be distributed along a gradient of frequency from ASD and intellectual disability at one end and BD at the other end of the spectrum (5). Large CNVs are significantly less strongly associated with BD relative to SCZ (18) but some evidence, albeit not definitive, suggests that they are particularly enriched among BD patients with early onset and greater cognitive impairment (5). This is in line with the idea of a broad neurodevelopmental gradient but also highlights the known heterogeneity within BD, again likely reflective of a greater neurodevelopmental load in a subgroup of BD patients.

Conclusions

Consistent with the idea of a neurodevelopmental continuum, evidence suggests that at least a subgroup of BD patients demonstrate early cognitive impairment, documented premorbidly and associated with a higher burden of large CNVs (5, 19). It is currently unclear whether early features of a neurodevelopmental disorder are associated with a specific phenotype in adulthood. We might hypothesise that individuals with a more pronounced set of childhood developmental features are more likely to develop BD with psychotic symptoms and a neurobiology closer to schizophrenia, in line with molecular imaging and genetic findings. Work on transdiagnostic dimensions highlights neurodevelopmental continuity between previously distinct constructs, with intellectual disability at one end of the spectrum

and BD at the other end. This work might also lead to identifying more homogenous and valid subcategories within the currently broadly defined disorders. This appears to be a critical step in bringing diagnostics closer to the underlying biological mechanisms.

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